Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/002108

International filing date: 28 February 2005 (28.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: SI
Number: P200400067
Filing date: 01 March 2004 (01.03.2004)

Date of receipt at the International Bureau: 16 March 2005 (16.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

REPUBLIKA SLOVENIJA
Ministrstvo za gospodarstvo

URAD REPUBLIKE SLOVENIJE ZA INTELEKTUALNO LASTNINO

Potrdilo

Certificate

Urad Republike Slovenije za intelektualno lastnino potrjuje, da je priloženi dokument istoveten z izvirnikom patentne prijave, kot sledi:

Slovenian Intellectual Property Office hereby certifies that the document annexed hereto is a true copy of the patent application, as follows:

(22) Datum prijave (*Application Date*):

1.3.2004 (1.mar.2004)

(21) Številka prijave (*Application No.*):

P-200400067

(54) Naziv (*Title*):

- Farmacevtska formulacija

Za izdajo tega potrdila je bila plačana taksa v višini 255,00 SIT po prvi alinei tarifne številke 4 taksne tarife Zakona o upravnih taksah (Uradni list RS, št. 8/00 in nadaljnji).

Ljubljana, 25.11.2004

REPUBLIKA SLOVENIJA MINISTRSTVO ZA GOSPODARSTVO Urad Republike Slovenije za intelektualno lastnino LJUBLJANA 4

Janez Kukec-Mezek
podsekretar

REPUBLIKA SLOVENIJA URAD RS ZA INTELEKTUALNO LASTNINO

Kotnikova 6, 1001 Ljubljana, p.p. 206, telefon: 01/478 3100, faks: 01/478 3111

REPUBLIKA SLOVENIJA
MINISTRSTVO ZA GOSPODARSTVO

URAD REPUBLIKE SLOVENIJE
ZA INTELEKTUALNO LASTNINO
1000 LJUBLJANA, KOTNIKOVA 6

ZAHTEVA ZA PODELITEV PATENTA

1. Naslov za obveščanje:

Lek farmacevtska družba d.d.

Sektor intelektualna lastnina

Verovškova 57

1526 Ljubljana

tel.: (01) 580 20 05
faks: (01) 568 21 23 šifra: 33668/SI/PSK

Potrdilo o prejemu prijave
(izpolni urad)

Datum vložitve prijave: 1. 3. 2004

Številka prijave: P- 20040006 7

Žig urada in podpis:

2. Prijavitelj (priimek, ime in naslov, za pravne osebe firma in sedež):

Lek farmacevtska družba d.d.
Verovškova 57
1526 Ljubljana

3. Zastopnik: Registrska številka:

4. Izumitelj (priimek, ime in naslov):

Svete Peter, Gradišnikova 14, 1353 Borovnica

5. Naziv izuma:

Farmacevtska formulacija

6. Podatki o zahtevani prednostni pravici in podlagi zanjo:

7. Dodatne zahteve:
- ☐ prijava je za patent s skrajšanim trajanjem
- ☐ predhodna objava patenta po preteku ____ mesecev
- ☐ prijava je izločena iz prijave številka:

8. Izjava:
- ☐ izjava o skupnem predstavniku:

9. Priloge:
- ☒ opis izuma, ki ima 17 strain 2x
- ☒ patentni zahtevek (zahtevki), ki ima(jo) 2 strani; število zahtevkov: 17 2x
- ☐ skice (če so zaradi opisa izuma potrebne); število listov: ____
- ☒ povzetek 2x
- ☐ potrdilo o plačilu prijavne pristojbine
- ☐ potrdilo o deponiranju biološkega materiala, če gre za izum, ki ga ni mogoče drugače opisati
- ☐ pooblastilo zastopniku
- ☐ generalno pooblastilo zastopniku je deponirano pri uradu pod št.: ____
- ☐ potrdilo o razstavni prednostni pravici
- ☐ podatki o drugih prijaviteljih
- ☐ podatki o drugih izumiteljih
- ☐ prikaz zaporedja nukleotidov ali aminokislin v opisu
- ☐ prijava je bila predhodno posredovana po faksu ali v elektronski obliki
- ☐ ____

REPUBLIKA SLOVENIJA
MINISTRSTVO ZA GOSPODARSTVO
URAD RS ZA INTELEKTUALNO LASTNINO

Prejeto dne: 01 -03- 2004 Osebna oddaja: ☒

Podpis: Oddano priporočeno dne:

Košak Alenka

Priimek in ime ter podpis prijavitelja (zastopnika

Podatki o drugih izumiteljih:

Grahek Rok
Kališka 9
4000 Kranj

Humar Vlasta
Godič 63
1242 Stahovica

Husu-Kovačević Breda
Na peči 27
1000 Ljubljana

PHARMACEUTICAL FORMULATION

Field of the Invention

(IPC[7] A 61 K)

The disclosed invention lies within the field of organic chemistry and pharmaceutical industry, and relates to new method of stabilization of the pharmaceutical active ingredient particularly one contained in a pharmaceutical formulation comprising an active pharmaceutical ingredients in a polymorph form which needs to be stabilized against converting into other polymorph forms.

Technical Problem

It is desirable to achieve a dosage form i.e. a tablet fulfilling following criteria: adequate flowability of the formulation; readily availability of the active ingredient as needed, (hence the tablets must have the proper type of drug release and the appropriate dissolution characteristics); appropriate solubility, physical and chemical stability of the formulation as such and of the therein contained active pharmaceutical ingredient, (which is sensitive to environmental influences i.e. humidity or moisture, heat, light, for which proper choice of method of manufacture and selection of excipients that is inactive ingredients is critical); mechanical integrity (to withstand damage during manufacturing, packaging, shipping and use).

Especially desirable is to prepare a stable finished dosage form and to stabilize the active pharmaceutical ingredient contained therein.

State of the Art

Many substances undergoing pharmaceutical processing are amorphous. Spontaneous crystallization and consequently a change of physical or chemical characteristics can occur under certain storage conditions, for example by exposure to environmental influences such as temperature and humidity. The tendency to appear in different polymorph forms is known in many types of active pharmaceutical ingredients for example in angiotensin II inhibitors where for example irbesartan or losartan appear in different polymorph forms or for example in atorvastatin and pravastatin which are known to exist in some ten polymorph forms, Metastable polymorphs are exemplified in Byrn S.R., Pfeiffer R.R. and Stowell J.G.: Solid-State Chemistry of Drugs, second ed., SSCI, Inc., West Lafayette, Indiana, 1999 (p. 143-231)

One of those active pharmaceutical ingredients is 2-n-butyl-4-chloro-5-hidroxymethyl-1-[[2'-(1H-tetrazole-5-yl)[1.1'-biphenyl]-4-yl]-1H-imidazole, known by the generic name losartan which can be used as an effective anti-hypertensive in form of its potassium salt incorporated into finished dosage form. It is known that potassium salt of losartan exists in at least two anhydrous polymorph forms which interconvert. [Pharm. Res. 10 (1993). 900] and according to WO 03048135 there are known amorphous losartan potassium and polymorph with bound between 12% and 16% of water as well as other forms.

Substituted imidazoles with effect on rennin-angiotensin system of blood pressure regulation, which include losartan, were disclosed in patent EP 253310 where formulation containing 20.41% active ingredient, 0.04 % SiO_2, 1.02 % magnesium stearate, 56.12 % microcrystalline cellulose, 2.25% starch and 20.16 % lactose was disclosed, patent does not disclose which polymorph was incorporated into finished formulation..

Alternative formulation of losartan potassium was disclosed in WO 9219228 where 10 – 45 % of an active ingredient was combined with 20 – 40 % of microcrystalline cellulose, 10 – 30 % latose, 0.5 – 0,9 % of a salt of steraic acid or talc, and 5 – 35 % pregel starch where such formulation was prepared by direct compression.

Losartan potassium intended for immediate release is marketed in form of talc polished coated tablets, and need to stabilize the active ingredient in bulk or in an exposed tablet core has not yet been recognized.

Another alternative pharmaceutical compositions were disclosed in WO 9943306, WO 9944590, WO 03035177, WO 03035039 and WO 03035029.

Yet alternative approach to formulating angiotensin II antagonist was disclosed in WO 02080910 by encapsulation in cyclodextrins or liposomes or biodegradable polymers.

Water absorbed by amorphous solids lowers the glass transition temperature of the solid, acts as plasticizer and increases molecular mobility, and the tendency of such absorbed water is to enhance the rate and extent of crystallization. [Chem. Pharm. Bull., 28, 2565-2569 (1980).]

Similar behavior as for amorphous matter can be expected for metastabile polymorphs, those are that polymorph forms that under specific conditions e.g. under environmental influences such as elevated temperature and high relative humidity can intercovert i.e. crystallize into more stable form.

A drug can be stabilized in solid dispersions whereby the drug is dispersed in a polymer matrix. Polymers inhibits crystallization by specific chemical interactions like hydrogen bonding, ion-dipole interactions or inclusion complex. Materials, which usually inhibit crystallization, are: polymers (polyvinylpyrrolidone (PVP),

cross-linked PVP, PVP/VA, polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), MC, HPC, CMEC, HPMC phthalate, microcrystalline cellulose (MCC), Dextran, Eudragits RS and RL); polymers/Surfactants; lipids; sugars (sucrose, dextrose, galactose); citric acid; cyclodextrins (HP-beta-CD, beta-CD)

Detailed Description of the Invention

The interconversions among the polymorph forms influence physical and chemical properties of the active pharmaceutical ingredient, which is often one of the most abundant ingredients in the formulation. It is not desired that such an interconversion occurs within the prepared finished dosage form.

Present invention describes a new method of stabilization of the pharmaceutical active ingredient. Pharmaceutical ingredient can be stabilized in bulk or contained in a pharmaceutical composition. Preferably the pharmaceutical composition is a unit dose pharmaceutical composition, which can be embodied in the form of tablets, capsules, pellets, granules, and suppositories or their combined forms. Solid pharmaceutical compositions can preferably be shielded that is protected from the surroundings, for example coated.

During our experimental work we have discovered that water present as moisture is one of the causes for intercoversions of polymorph forms.

In our experiments on angiontensin II inhibitors we have noticed that under the influence of absorbed water the amorphous potassium salt of losartan crystallizes and polymorph from X (polymorph form exhibiting strongest diffractions in powder X-ray difractogram at around $2\theta = 6.9$, 13.8, 20.6, 24.0, 24.8, 28.7 and 29,2 °) of potassium salt of losartan interconverts into others polymorph forms. There is a need to prevent solid-solid transformation into others polymorph forms.

We have devised two general approaches to reach the goal. One is to prevent water to diffuse to the surface of particles of the active pharmaceutical ingredient and the other is to stabilize the surface with abovementioned polymers.

For the first approach to temporarily stabilize active pharmaceutical ingredient we have chosen substances, which absorb or chemically bind water molecules fast and strong enough to prevent water absorption to the surface of particles of active pharmaceutical ingredient, for example: calcium chloride, sodium phosphate, sodium or magnesium sulphate, magnesium oxide or calcium oxide, or silicium dioxide, for example colloidal silicium dioxide (SiO_2), for example sold under trade name Aerosil, which is an adsorbent, anticaking agent, glidant, suspending agent, tablet disintegrant and viscosity-increasing agent or anhydrous silicium dioxide, preferably a finely divided silicium dioxide, for example sold under trade name: Syloid, which is amorphous powder characterized by an internal structure of sponge like pores. Three important characteristics determine the behaviour of the various Syloid grades: porosity, average particle size, the surface treatment. Several grades of Syloid are commercially available. On the base of physical and chemical characteristics the AL-1 type was selected. The Syloid AL-1 (Grace Davison) is the grade having the finest pores and the largest specific area.

Silicium dioxide is widely used in pharmaceuticals, cosmetics and food products in hydrated or anhydrous form.

Said approach can be further improved by preventing water or moisture reaching thus formed mixture by forming tablets thereof and coating them with a coating that is hardly permeable by water. Such coating should nevertheless posses certain physical properties allowing release of drug when ingested.
The second approach is based on use of polivynylpyrolidone or polyethyleneglycol (for example: PVP K-25 and PEG 6000) in wet granulation together with a

metastable active pharmaceutical ingredient with suitable solvent to surround every respective particle with polymer shield. Stabilizing effect can be further ameliorated by coating of finished dosage form.

An embodiment of present invention is thus a method of stabilization of an active pharmaceutical ingredient in a polymorph form that is susceptible to intercovert or crystallize into other polymorph form by incorporation of stabilizing substances.

Stabilization of bulk active pharmaceutical ingredient or pharmaceutical ingredient contained in a finished pharmaceutical dosage form

It is common practice to produce an active pharmaceutical ingredient in a metastable polymorph form. Such polymorph, for example an amorphous substance is needed to achieve readily availability of the active ingredient when formulated.

Amorphous losartan potassium or occurring in polymorph form X is very sensitive to humidity and converts quickly into other polymorph forms, preferably into form I.

In one embodiment of our invention an active pharmaceutical ingredient in an metastable polymorph form is stabilized using inactive ingredients that protect it from humidity, for example by admixing active pharmaceutical ingredient with an inactive ingredient as described below.

Preferably amorphous or form X of losartan potassium is stabilized using inactive ingredients that achieve the stabilizing effect for example by protecting substance from environmental influences, for example humidity. The most affected stabilization is achieved with for example: SiO_2, MgO, CaO, polyethylene glycol, Ac-di-sol, Prosolv, Aerosil, preferably with Prosolv and Ac-di-sol, which protect substance preferably under more controlled humidity conditions in closed

packaging, and most preferably with Syloid, MgO and PEG 6000 in ratio up to 50%, or up to about 25% preferably up to 12.5%, preferably from about 1% to about 10%, most preferably in certain embodiments from about 1% to about 3% of inactive ingredient.

Addition of stabilizing substance selected from the group comprising Syloid, MgO and PEG 6000 does not stabilize the active pharmaceutical ingredient only temporarily while the stabilizing substance binds water, but surprisingly also after the mixture being exposed to 60% relative humidity after days when the stabilizing substance was already saturated with water. Thus.said inactive ingredients can prevent the conversion of a pharmaceutical active substance into another polymorphic form under the influence of constantly humidity of or exceeding 60% and high water content in samples.

Preparation of finished dosage forms

Conversion of a pharmaceutical active substance contained in a finished dosage form into another polymorphic form under the environmental influences can be prevented by shieldind the conventionally prepared dosage form for example by applying a film coating.

Alternatively one of the embodiments of present invention is a pharmaceutical composition which is a finished dosage form that contains up to 50%, preferably up to about one quarter most preferably from about 1% to about 10% or from about 3% to about 5% of the finished dosage form of the inactive ingredient, which achieves stabilizing effect as described above.

In another embodiment a conventionally prepared dosage form is film coated with a coat thus being able to withstands damage during packaging, shipping and use and yet still provides the appropriate dissolution characteristics and drug release.

Thus a solid unit dosage form can be prepared by any suitable method from pharmaceutical active ingredient in polymorph form that may convert into other polymorph forms for example a solid unit dosage form of losartan by direct compression from mixture of amorphous or form X of losartan potassium and pharmaceutically acceptable excipients. The dosage form thus formed is film coated with a coat comprising stearic acid,

Presence of stearic acid surpassingly yields coat, that due to its physical (elasticity) and chemical properties provides for the maximum protection of the cores comprising an active pharmaceutical ingredient in a polymorph forms that under specific conditions e.g. temperature and relative humidity can intercovert i.e. crystallize into other forms.

The coating of different thickness can be applied. Usually a coating up to one tenth, preferably from about 3% to about 9%, by weight relative to core weight is applied.

In one embodiment of present invention finished dosage form is prepared which contains up to about 10 % in one embodiment from about 1% to about 10%, alternatively from about 1% to about 3% or alternatively from about 3% to about 10% of anhydrous silicium dioxide.

In a preferred embodiment a finished dosage form is an oral finished dosage form comprising active pharmaceutical ingredient in a polymorph forms that intercovert i.e. crystallize into more stable form, preferably comprising potassium salt of losartan in amount from one quarter to one half by weight, most preferably in amount of about 30% and further comprising from about half to about two thirds by weight, preferably about 60% silicified microcrystalline cellulose; from about 2% to about 5% by weight, preferably about 4% of an disintegrant for example

croscamellose sodium; up to about 1.5%, preferably about 0.5% meagnesium stearate or any other suitable lubricant and up to about 10 % preferably from about 1% to about 10%, most preferably around 3% of anhydrous silicium dioxide.

In a most preferred embodiment of present invention the cores of the finished dosage form prepared with an inactive ingredient, which achieves stabilizing effect as, described above are film coated with coat comprising stearic acid. The weight ratio of stearic acid in coat relative to weight of whole finished dosage form is from 0.1% to about 1.7%, preferably from 0.2% to 0.9%. most preferably about 0.6%.

The embodiments of the present invention are thus: an active pharmaceutical ingredient in a polymorph form susceptible to degradation or interconversion into other polymorph forms stabilized by a stabilizing substance.In one of the embodiments a stabilizing substance is selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol. Further the invention is embodied in a pharmaceutical composition comprising an active pharmaceutical ingredient in a polymorph form susceptible to degradation or interconversion into other polymorph forms characterized by comprising also a stabilizing substance selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol and/or embodied in a pharmaceutical composition characterized in that it is coated with a film coating comprising stearic acid in amount from about 0.1% to about 1.7% by weight of the of the pharmaceutical composition.

In a specific embodiment, the invention is a potassium salt of losartan in a polymorph form susceptible to degradation or interconversion into other polymorph forms stabilized by a stabilizing substance selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol.

In an embodiment invention is a pharmaceutical composition as decribed above where the stabilizing substance is finely divided anhydrous silicium dioxide present in amount of about 1 % to about 10% by weight. Ina preferred embodiment finely divided anhydrous silicium dioxide is a syloid.

Embodiments of the invention are also a method of stabilization of an active pharmaceutical ingredient, which is susceptible to degradation or interconversion causing change of physical or chemical properties where an active pharmaceutical ingredient is stabilized by adding a finely divided silicium dioxide and/or magnesium oxide and/or polyethylene glycol. Specifically a method of stabilization of an active pharmaceutical ingredient in a polymorph forms that is susceptible to intercovert or crystallize into other polymorph form by a stabilizing substance selected from a group comprising finely divided silicium dioxide, magnesium oxide, polyethylene glycol.

Embodiment of the invention is also a use of finely divided silicium dioxide for the stabilization of an active pharmaceutical ingredient to prevent the transition of the active pharmaceutical ingredient among polymorph forms.

Preferably in above embodiments the stabilizing substance is a syloid, specifically Syloid AL-1 or polyethylene glycol specifically PEG 600.

The following Examples further illustrate the invention. They are provided for illustrative purposes only, and are not intended to limit the invention in any way

Examples

Experiments in order to select potential inactive ingredients that could stabilize metastable polymorph form of an active ingredient and prevent conversion into other polymorph forms.

Mixtures of potassium salt of losartan (losartan potassium) polymorph form X with different inactive ingredients were tested under the influence of humidity under the below described stability study protocol and are presented in a Table 1.

Storage conditions:

1. Open dish study - constant influence of humidity

Testing mixtures were put into open petri dishes and were stored in a thermostatically controlled chamber at a temperature of 25 °C (±2 °C) and 60 % (±5 %) relative humidity

2. Vial study - influence of humidity in a closed container (simulation of packaging)

Testing mixtures were put into vials, exposed to 60 % humidity for 18 hours, than closed with rubber stoppers and stored in a thermostatically controlled chamber at temperature of 25 °C (±2 °C) and 60 % (±5 %) relative humidity.

Duration of study and time points:

Mixtures were tested up to 5 days in open petri dishes and up to 4 and 9 days in vials. and were analysed in few days' intervals or until the significant change occurred.

Testing parameters

1. Appearance
2. Lost on drying
3. Polymorph form

Powder X-ray diffraction spectra is most characteristic testing parameter that indicates stability of polymorph form and was determined at selected time points for all testing mixtures and active ingredient itself.

Mixtures	Weight ratio
Losartan potassium form X : Syloid (Silica Colloidalis Anhydrica)	2:1
Losartan potassium form X:MgO (Magnesium oxyde)	2:1
Losartan potassium form X : PVP K-25	4:1
Losartan potassium form X:PEG 6000	4:1
Losartan potassium form X:Lactose (Lactose Anhydrica)	1:1
Losartan potassium form X:Ac-di-sol (Croscarmellose sodium)	1:1
Losartan potassium form X:Mg stearate (Magnesium stearate)	1:1
Losartan potassium form X:Prosolv (Silicified Microcryst. Cellulose)	1:1
Losartan potassium form X:Aerosil (Silica Colloidalis)	1:1
Losartan potassium form X substance	/

Table 1: Mixtures of potassium salt of losartan polymorph form X with different inactive ingredients

Results are presented in Tables 3 and 4 and are compared to not stabilized active ingredient presented in a Table 2.

Testing parameter	Storage conditions and time points			
	Initial state	open dish, 5 days	vial, 4 days	vial, 9 days
Appearance	white powder	white slightly sticky powder	white slightly sticky powder	white slightly sticky powder
Lost on drying	0.08 %	0.93 %	0.52 %	
Polymorph form	Form X, Form I was not detected	Form X + 10 % form I was detected	Form X + 5 % form I was detected	Form X was completely converted into form I

Table 4: Changes occurring in not stabilized losartan potassium form X

Different inactive ingredients were tested in mixtures with API polymorph form X under the stress conditions of constantly 60 % humidity and under humidity trapped into closed container (vials).

The results demonstrate the following:

- Mixtures with Syloid and PEG 6000 showed very good results since Losartan potassium remained in form X completely after 4 days in vials and after 5 days at constantly 60 % relative humidity, which is more stressed situation, not more than 1-2 % conversion of form x into form I occurred. The stabilisation effect occurred even thought water content increased up to 3.5-7 %. Surprisingly in an equivalent experiment by using PVP K-25 instead of PEG 6000 Losartan potassium form X was completely converted into form I after 4 days in vial that indicate the destabilization of metastable polymorph form.
- Results are very similar for mixtures with MgO, only 1-2 % conversion was detected in vials after 4 days and up to 3 % after 5 days in an open petri dish.
- Binary mixtures with lactose, Ac-di-sol, Mg Stearate, Prosolv and Aerosil were tested for 9 days in vials. Losartan potassium form X was almost completely converted into form I in mixtures with Lactose and Mg Stearate, in mixture with Aerosil beside form I amorphous form was detected as well.
- For mixtures with Prosolv and Ac-di-sol no conversion of form X into form I was determined.

losartan potassium form X : Syloid 2:1 mixture

Testing parameter	Storage conditions and time points		
	Initial state	vial, 4 days	open dish, 5 days
Appearance	white powder	white powder	white powder
Lost on drying	0.21 %	6.7 %	7.0 %
Polymorph form	Form X, Form I was not detected	Form X, Form I was not detected	Form X + 1-2 % form I was detected

losartan potassium form X : MgO 2:1 mixture

Testing parameter	Storage conditions and time points		
	Initial state	vial, 4 days	open dish, 5 days
Appearance	white powder	white powder	white powder
Lost on drying	0.03 %	0.4 %	1.4 %
Polymorph form	Form X, Form I was not detected	Form X + 1-2 % form I was detected	Form X + 2-4 % form I was detected

losartan potassium form X : PEG 6000 4:1 mixture

Testing parameter	Storage conditions and time points		
	Initial state	vial, 4 days	open dish, 5 days
Appearance	white powder	white slightly sticky powder	white sticky powder
Lost on drying	< 0.01 %	2.1 %	3.5 %
Polymorph form	Form X, Form I was not detected	Form X, Form I was not detected	Form X + 1-2 % form I was detected

losartan potassium form X : PVP K-25 4:1 mixture

Testing parameter	Storage conditions and time points		
	Initial state	vial, 4 days	open dish, 5 days
Appearance	white powder	white slightly sticky powder	white sticky powder
Lost on drying	1.8 %	3.9 %	4.9 %
Polymorph form	Form X, Form I was not detected	Form X was completely converted into form I	/

Table 3: Changes occurring in mixtures, Experiment no. 1 up to 5 days in open petri dishes and up to 4 days in vials.

losartan potassium form X : Lactose 1:1 mixture

Testing parameter	Storage conditions and time points	
	Initial state	vial, 9 days
Appearance	white powder	white powder
Lost on drying	0.06 %	0.17 %
Polymorph form	Form X, Form I was not detected	Form X was completely converted into form I

losartan potassium form X : Ac-di-sol 1:1 mixture

Testing parameter	Storage conditions and time points	
	Initial state	vial, 9 days
Appearance	white powder	white powder
Lost on drying	< 0.01 %	5.42 %
Polymorph form	Form X, Form I was not detected	Form X, Form I was not detected

losartan potassium form X : Mg stearate 1:1 mixture

Testing parameter	Storage conditions and time points	
	Initial state	vial, 9 days
Appearance	white powder	white powder
Lost on drying	1.65 %	1.16 %
Polymorph form	Form X, Form I was not detected	Form X was completely converted into form I

losartan potassium form X : Prosolv 1:1 mixture

Testing parameter	Storage conditions and time points	
	Initial state	vial, 9 days
Appearance	white powder	white powder
Lost on drying	0.11 %	3.11 %
Polymorph form	Form X, Form I was not detected	Form X, Form I was not detected

losartan potassium form X : Aerosil 1:1 mixture

Testing parameter	Storage conditions and time points	
	Initial state	vial, 9 days
Appearance	white powder	white powder
Lost on drying	0.36 %	1.11 %
Polymorph form	Form X, Form I was not detected	Form X was partially converted into form I and partially into amorphous form

Table 4: Changes occurring in mixtures, Experiment no. 2 up to 9 days in vials.

Film coated pharmaceutical composition comprising active ingredient stabilized against interconversion of polymorph form

Experimental tablets were prepared by direct compression method. The formula contained 100 mg of losartan potassium per tablet in 320 mg tablets. The percentage of Syloid AL-1 in formula is between 3 and 5%. The compaction behaviour of the losartan is not very good so the excipients selection is based on enhancing flow, and improving compactibility. Silicified Microcrystalline Cellulose was found to have excellent compactibility and achieved high dose loading, further croscarmellose sodium is added as a disintegrant. Magnesium stearate is selected in this formulation as an excellent lubricant. The quantity from 0.5 to 1.0 % is necessary in the formulation to make compression feasible. Tablets are film coated.

core	mg/tablet	% of core
Losartan potassium	100.00	31.25
Silicified Mycrocrystalline Cellulose	195.60	61.12
Silica Colloidalis Anhydrica	10.00	3.13
Croscarmellose sodium	12.80	4.00
Magnesium stearate	1.60	0.50
	320.00	100.00

coating	mg/tablet	% relative to core
Hydroxypropylcelliulose	10.90	3.24
Stearic acid	2.10	0.62
Triethyl citrate	0.80	0.24
Titanium dioxide	1.08	0.32
Ferric oxide red	0.02	0.01
Talc	1.10	0.33
	16.00	4.76

Preparation procedure of cores:

Losartan potassium and silica coloidalis anhydrica are mixed, than

silicified mycrocrystalline cellulose and croscarmelose sodium are added and homogenised by mixing for 10 minutes. The dry mixture is sieved before Magnesium stearate is added and the final mixture is blending for 3 min.
The final dry mixture is compressed on a rotary tableting machine.
The tablets produced have weight 320 mg, diameter 10mm, and have satisfactory technical properties.

Coating:

Hydroxypropylcellulose and triethyl citrate are dissolved while stirring in ethanol, and then homogenised (Ultraturax, 30 min.) dispersion of titanium dioxide , ferric oxide red, stearic acid and talc in ethanol is added.
Prepared dispersion is sprayed onto cores so the film coating in a weight ratio of about 4,8 wt.% regard to the core is obtained. Tablets are also polished with talc.

Claims

1. An active pharmaceutical ingredient in a polymorph form susceptible to degradation or interconversion into other polymorph forms stabilized by a stabilizing substance selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol.

2. Potassium salt of losartan in a polymorph form susceptible to degradation or interconversion into other polymorph forms stabilized by a stabilizing substance selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol.

3. A pharmaceutical composition characterized in that it is coated with a film coating comprising stearic acid in amount from about 0.1% to about 1.7% by weight of the of the pharmaceutical composition.

4. A pharmaceutical composition comprising an active pharmaceutical ingredient in a polymorph form susceptible to degradation or interconversion into other polymorph forms characterized by comprising also a stabilizing substance selected from a group comprising: finely divided silicium dioxide, magnesium oxide or polyethylene glycol.

5. A pharmaceutical composition according to preceding claim where the stabilizing substance is finely divided anhydrous silicium dioxide or polyethylene glycol present in amount of about 1 % to about 10% by weight

6. A pharmaceutical composition according to claim 4 or 5 comprising potassium salt of losartan.

7. A pharmaceutical composition according to any one of claims 4 to 6 which is a finished dosage form comprising potassium salt of losartan and from about 1% to about 10% of syloid.

8. A pharmaceutical composition according to previous claim which is a finished dosage form comprising potassium salt of losartan and from about 3% to about 10% of syloid.

9. A pharmaceutical composition according to any one of claims 4 to 8 characterized in that it is coated with a film coating comprising stearic acid in amount from about 0.1% to about 1.7% by weight of the whole pharmaceutical composition.

10. A method of stabilization of an active pharmaceutical ingredient, which is susceptible to degradation or interconversion causing change of physical or chemical properties where an active pharmaceutical ingredient is stabilized by adding a finely divided silicium dioxide and/or magnesium oxide and/or polyethylene glycol.

11. A method of stabilization of an active pharmaceutical ingredient in a polymorph forms that is susceptible to intercovert or crystallize into other polymorph form by a stabilizing substance selected from a group comprising finely divided silicium dioxide, magnesium oxide, polyethylene glycol.

12. Use of finely divided silicium dioxide for the stabilization of an active pharmaceutical ingredient to prevent the transition of the active pharmaceutical ingredient among polymorph forms.

Lek farmacevtska družba d.d.

Povzetek:

Aktivne farmacevtske učinkovine dovzetne za prehode med polimorfi se da stabilizirati s primernimi stabilizirajočimi substancami kot so fino porazdeljen silicijem dioksid, magnezijev oksid ali polietilen glikol. Tudi farmacevtske pripravke vsebujoče aktivne farmacevtske učinkovine dovzetne za prehode med polimorfi se da stabilizirati na ta način in/ali z oblaganjem z oblogo na osnovi stearinske kisline.